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L15: Entry 9 of 9

File: USPT

May 30, 1989

DOCUMENT-IDENTIFIER: US 4834076 A

TITLE: Device for treating the external human epithelium, process for its manufacture and process for using such a device

Brief Summary Text (16):

According to the invention, the active substance contained in the latter is chosen to contain one or more agents with a therapeutic and/or cosmetological action which are active in skin treatment, in particular treatment of the phenomena associated with aging, such as wrinkles on the face.

Detailed Description Text (27):

Among the biological derivatives of animal origin, derivatives of the substances constituting the intercellular matrix of the dermis are of particular value in caring for the skin, the scalp and the hair. These are especially fractions of macromolecules: keratin, collagen, elastin, mucopolysaccharides, proteoglycans and glycoproteins of structures, as well as phospholipids and lipoamino acids. Macroprotein hydrolysates consist particularly of amino acids and certain sugars or derivatives, for example hydroxyproline, desmosin, N-acetylglucosamine, glucuronic acid, glucosamine, tryptophan and cysteine. Of these substances, DL-methionine, S-carboxymethylcysteine and glucuronic acid are of particular value in caring for the scalp, as are cystine and methylcysteine sebacate.

Detailed Description Paragraph Table (4):

EXAMPLES: no. 13 no. 14 no. 15	
12% <u>Biotin</u> (vitamin H) 6% Cystine 10% A Essential vegetable oils 2% 1% Thiamine hydrochloride 0.5% Nicotinamide (vitamin PP) 0.9% Panthenol 0.7% Vitamin C 0.1% B Glycerol 10% Epoxidized soya oil 2% 2% 3% Calcium stearate 3% 2% C Dioctyl adipate (DOA) 25% Dibutyl phthalate 15% 24% Colorant 0.3% 0.3% Butadiene/acrylonitrile 2% 5% Polyvinyl chloride 59.5% 52.5% 54%	Vitamin A (acetate) 3% Vitamin E 2% Vitamin F

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L16: Entry 6 of 6

File: PGPB

Nov 15, 2001

DOCUMENT-IDENTIFIER: US 20010041718 A1

TITLE: Compositions and methods for treating conditions responsive to estrogen

Summary of Invention Paragraph (6):

[0005] Aromatase activity resides within a transmembrane glycoprotein (P.sub.450,arom) that is homologous with the cytochrome P.sub.450 family of monooxygenases (Nebert, D. W. and Gonzalez, F. J., Annu. Rev. Biochem. 56:945-993, (1987); Corbin, C. J., et al., Proc. Natl. Acad. Sci. USA, 85:8948-8952, (1988)); also essential is a ubiquitous flavoprotein, NADPH-cytochrome P.sub.450 reductase. Both proteins are localized in the endoplasmic reticulum of ovarian granulosa cells, testicular Sertoli and Leydig cells, adipocytes, placental syncytiotrophoblasts, the preimplantation blastocyst, and various brain regions, including the hypothalamus.

Detail Description Paragraph (179):

[0214] If the topical pharmaceutical and cosmetic compositions of the present invention are formulated as a gel or a cosmetic stick, a suitable amount of a thickening agent, as disclosed supra, is added to a cream or lotion formulation. The topical pharmaceutical and cosmetic compositions of the present invention may also be formulated as makeup products such as foundations. Foundations are solution or lotion-based with appropriate amounts of thickeners, pigments and fragrance. The topical pharmaceutical and cosmetic compositions of the present invention may contain, in addition to the aforementioned components, a wide variety of additional oil-soluble materials and/or water-soluble materials conventionally used in topical compositions, at their established levels. Various water-soluble materials may also be present in the compositions of this invention. These include humectants, such as glycerol, sorbitol, propylene glycol, alkoxylated glucose and hexanetriol, ethyl cellulose, polyvinylalcohol, carboxymethyl cellulose, vegetable gums and clays such as VEEGUM.RTM. (magnesium aluminum silicate, R. T. Vanderbilt, Inc.); proteins and poly peptides, preservatives such as the methyl, ethyl, propyl and butyl esters of hydroxybenzoic acid (Parabens.RTM.--Mallinckrodt Chemical Corporation), EDTA, methylisothiazolinone and imidazolidinyl ureas (Germall 115.RTM.--Sutton Laboratories); and an alkaline agent such as sodium hydroxide or potassium hydroxide to neutralize, if desired, part of the fatty acids or thickener which may be present. In addition, the topical compositions herein can contain conventional cosmetic adjuvants, such as dyes, opacifiers (e.g., titanium dioxide), pigments and perfumes. The topical pharmaceutical and cosmetic compositions of the present invention may also include a safe and effective amount of a penetration enhancing agent. A preferred amount of penetration enhancing agent is from about 1% to about 5% of the composition. Other conventional skin care product additives may also be included in the compositions of the present invention. For example, collagen, hyaluronic acid, elastin, hydrolysates, primrose oil, jojoba oil, epidermal growth factor, soybean saponins, mucopolysaccharides, and mixtures thereof may be used. Various vitamins may also be included in the compositions of the present invention. For example, Vitamin A, and derivatives thereof, Vitamin B2, biotin, pantothenic, Vitamin D, and mixtures thereof may be used.

Detail Description Paragraph (232):

[0261] The subject lays on his or her back with eyes closed. The measuring rod is adjusted to touch the skin and the baseline output of the LVDT transducer system recorded until stabilized. After the baseline is stabilized, a standard weight (sufficient to exert 10 g/cm.sup.2 force) is applied. Indentation of the measuring rod is recorded for 10 seconds and then the weight is removed from the measuring rod and the rebound is recorded for an additional 10 seconds. The percentage rebound is calculated by dividing rebound distance by total indentation. Using a range of weights on the measuring rod to achieve a pressure range of 10 to 100 g/cm.sup.2, a

.depth of indentation versus pressure curve is calculated for the test area of skin. The rebound and indentation versus pressure measurements are performed on the subject prior to dosing with an estrogen agonist/antagonist of the present invention. The subject is then dosed with estrogen agonist/antagonist or the subject is instructed to daily apply a topical composition comprising the estrogen agonist/antagonist of the present invention. Measurements of skin elasticity are repeated at 1, 3 and 6 months of dosing. An increase in skin elasticity associated with a reduction in wrinkles is indicated with an increased rebound score and steeper depth of penetration versus pressure relationship.

## WEST Search History

DATE: Monday, June 09, 2003

<u>Set Name</u> side by side	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u> result set
<i>DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ</i>			
L26	L25 and l2l	14	L26
L25	glycoprotein.clm.	2293	L25
L24	L23 and l2l	23	L24
L23	biotin.clm.	2704	L23
L22	L2l same l8	6	L22
L2l	skin same wrinkle\$	7002	L2l
L20	Ll9 same l8	9	L20
Ll9	wrinkle\$	46215	Ll9
Ll8	Ll same l8	1	Ll8
Ll7	Ll and l8	27	Ll7
Ll6	Ll and l8 and l9	6	Ll6
Ll5	Ll3 and l8 and l9	9	Ll5
Ll4	Ll3 and l5	0	Ll4
Ll3	skin ADJ TREATMENTS\$	3631	Ll3
Ll2	Ll1 same l8 and l9	10	Ll2
Ll1	skin same treat\$6	69811	Ll1
Ll0	skin	337978	Ll0
L9	glycoprotein	31295	L9
L8	biotin	32014	L8
L7	bitin	26	L7
L6	L5 and ll	0	L6
L5	biotin same glycoprotein	527	L5
L4	L3 and l2 and ll	0	L4
L3	glycoprotein.ti.	1339	L3
L2	biotin.ti.	950	L2
Ll	skin adj elasticity	620	Ll

END OF SEARCH HISTORY

09/701,196

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L16: Entry 5 of 6

File: PGPB

Jan 31, 2002

DOCUMENT-IDENTIFIER: US 20020012927 A1

TITLE: Nucleic acid sequences associated with aging, particularly skin aging

Summary of Invention Paragraph (6):

[0005] One particular manifestation of aging is skin aging. In addition to the intrinsic factors (i.e., age), skin aging has been shown to be due to a variety of extrinsic factors. Such extrinsic factors include, e.g., the sun's ultra violet rays, stress, pollution, diet, alcohol, tobacco, climate, air travel, environmental elements, etc. As skin cells undergo senescence, signs of skin aging appear, including, e.g., atrophy of the epidermis, decrease in the number of Langerhans cells, increased dryness of the skin, decrease in the number of cells in the dermis, decrease in elastic fibers and in skin elasticity, increased fragility of capillaries, slowing of collagen metabolism, lowering in the concentration of glycosaminoglycans, sagging of the skin, decreased ability to mount inflammatory responses, increased in the time of healing after injury, appearance of deep wrinkles, pigmentary alterations with areas of hyper- and hypopigmentation, appearance of a variety of benign, premalignant, and malignant neoplasms, etc.

Detail Description Paragraph (6):

[0021] In the context of the present invention, "aging" of a cell or tissue encompasses the aging processes due to intrinsic aging, as well as disease- or extrinsic factors-related aging. "Aging" of a cell or tissue is characterized by, e.g., cell death (senescence) and loss of cell proliferation potential, as well as any of a number of characteristic structural and/or molecular features. In the context of the present invention, "aging" refers to all the stages of the process. "Skin aging" might be correlated with specific structural properties, such as, e.g., appearance of deep wrinkles, pigmentary alterations, atrophy of the epidermis, increased dryness of the skin, decrease in the number of cells in the dermis, decrease in elastic fibers and in skin elasticity, increased fragility of capillaries, appearance of neoplasms, etc.

Detail Description Paragraph (37):

[0052] The probes are typically labeled either directly, as with isotopes, chromophores, lumiphores, chromogens, or indirectly, such as with biotin, to which a streptavidin complex may later bind. Thus, the detectable labels used in the assays of the present invention can be primary labels (where the label comprises an element that is detected directly or that produces a directly detectable element) or secondary labels (where the detected label binds to a primary label, e.g., as is common in immunological labeling). Typically, labeled signal nucleic acids are used to detect hybridization. Complementary nucleic acids or signal nucleic acids may be labeled by any one of several methods typically used to detect the presence of hybridized polynucleotides. The most common method of detection is the use of autoradiography with <sup>3</sup>H, <sup>125</sup>I, <sup>35</sup>S, <sup>14</sup>C, or <sup>32</sup>P-labeled probes or the like.

Detail Description Paragraph (38):

[0053] Other labels include, e.g., ligands which bind to labeled antibodies, fluorophores, chemi-luminescent agents, enzymes, and antibodies which can serve as specific binding pair members for a labeled ligand. An introduction to labels, labeling procedures and detection of labels is found in Polak and Van Noorden Introduction to Immunocytochemistry, 2nd ed., Springer Verlag, NY (1997); and in Haugland Handbook of Fluorescent Probes and Research Chemicals, a combined handbook and catalogue Published by Molecular Probes, Inc. (1996). Primary and secondary labels can include undetected elements as well as detected elements. Useful primary and secondary labels in the present invention can include spectral labels such as

- fluorescent dyes (e.g., fluorescein and derivatives such as fluorescein isothiocyanate (FITC) and Oregon Green.TM., rhodamine and derivatives (e.g., Texas red, tetra-rhodamine isothiocyanate (TRITC), etc.), digoxigenin, biotin, phycoerythrin, AMCA, CyDyes.TM., and the like), radiolabels (e.g., sup.3H, sup.125I, sup.35S, sup.14C, sup.32P, sup.33P, etc.), enzymes (e.g., horse radish peroxidase, alkaline phosphatase etc.), spectral colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads. The label may be coupled directly or indirectly to a component of the detection assay (e.g., the probe) according to methods well known in the art. As indicated above, a wide variety of labels may be used, with the choice of label depending on the sensitivity required, the ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions.

Detail Description Paragraph (65):

[0080] In a preferred embodiment, the labeling agent is a second antibody bearing a label. Alternatively, the second antibody may lack a label, but it may, in turn, be bound by a labeled third antibody specific to antibodies of the species from which the second antibody is derived. The second antibody can be modified with a detectable moiety, such as biotin, to which a third labeled molecule can specifically bind, such as enzyme-labeled streptavidin.

Detail Description Paragraph (69):

[0084] Immunoassays for detecting proteins of interest from tissue samples may be either competitive or noncompetitive. Noncompetitive immunoassays are assays in which the amount of captured analyte (in this case the protein) is directly measured. In one preferred "sandwich" assay, for example, the capture agent (e.g., anti-skin aging-associated protein antibodies) can be bound directly to a solid substrate where it is immobilized. These immobilized antibodies then capture the aging-associated protein present in the test sample. The aging-associated protein thus immobilized is then bound by a labeling agent, such as a second anti-aging-associated protein antibody bearing a label. Alternatively, the second antibody may lack a label, but it may, in turn, be bound by a labeled third antibody specific to antibodies of the species from which the second antibody is derived. The second can be modified with a detectable moiety, such as biotin, to which a third labeled molecule can specifically bind, such as enzyme-labeled streptavidin.

Detail Description Paragraph (83):

[0098] Non-radioactive labels are often attached by indirect means. Generally, a ligand molecule (e.g., biotin) is covalently bound to the molecule. The ligand then binds to an anti-ligand (e.g., streptavidin) molecule which is either inherently detectable or covalently bound to a signal system, such as a detectable enzyme, a fluorescent compound, or a chemiluminescent compound. A number of ligands and anti-ligands can be used. Thyroxine, and cortisol can be used in conjunction with the labeled, naturally occurring anti-ligands. Alternatively, any haptenic or antigenic compound can be used in combination with an antibody.

Detail Description Paragraph (115):

[0130] Retroviral vectors are also useful for introducing the nucleic acids of the invention into target cells or organisms. Retroviral vectors are produced by genetically manipulating retroviruses. The viral genome of retroviruses is RNA. Upon infection, this genomic RNA is reverse transcribed into a DNA copy which is integrated into the chromosomal DNA of transduced cells with a high degree of stability and efficiency. The integrated DNA copy is referred to as a provirus and is inherited by daughter cells as is any other gene. The wild type retroviral genome and the proviral DNA have three genes: the gag, the pol and the env genes, which are flanked by two long terminal repeat (LTR) sequences. The gag gene encodes the internal structural (nucleocapsid) proteins; the pol gene encodes the RNA directed DNA polymerase (reverse transcriptase); and the env gene encodes viral envelope glycoproteins. The 5' and 3' LTRs serve to promote transcription and polyadenylation of virion RNAs. Adjacent to the 5' LTR are sequences necessary for reverse transcription of the genome (the tRNA primer binding site) and for efficient encapsulation of viral RNA into particles (the Psi site). See, Mulligan, In: Experimental Manipulation of Gene Expression, Inouye (ed), 155-173 (1983); Mann et al., Cell 33:153-159 (1983); Cone and Mulligan, Proceedings of the National Academy of Sciences, U.S.A., 81:6349-6353 (1984).

## Detail Description Table CWU (1):

TABLE 1 LifeSpan Image Gene Name Cluster ID CloneID 5' ESTID 3' ESTID COMMENT

Mast/stem cell growth factor receptor 3041 37621 R35401 Upregulated in Young Skin

Tyrosine kinase elk1 1565 48213 H11855 Upregulated in Young Skin Ls138820 138820

25656 R11996 R39835 Upregulated in Young Skin Probable ubiquitin carboxyl-terminal hydrolase ubp0 3887 25765 R12305 R37236 Upregulated in Young Skin Ls39545 39545

26230 R12449 R37335 Upregulated in Young Skin Oligopeptide transporter, kidney isoform 3535 26394 R12865 R38438 Upregulated in Young Skin Axonin-1 583 28510 R14151

R40446 Upregulated in Young Skin Hypothetical protein KIAA0194 2422 29851 R15164

R41584 Upregulated in Old Skin Nociceptin receptor 3452 32221 R17579 Upregulated in Young Skin Semaphorin-III (hsema-I) 9909 33664 R19784 Upregulated in Young Skin Ls138982 138982 36125 R21084 R46260 Upregulated in Young Skin Carboxypeptidase E 847 36500 R25556 R46713 Upregulated in Young Skin Breast cancer, estrogen regulated liv-1 protein (liv-1) 8033 43444 H13013 H05907 Upregulated in Young Skin Ls25730 25730 45021 H08058 H08059 Upregulated in Young Skin Ls141258 141258 46429 H09683 H09647 Upregulated in Young Skin Ls56848 56848 47544 H11535 Upregulated in Young Skin Histone deacetylase 1 2130 67146 T56773 T56772 Upregulated in Young Skin Calcizzarin 792 70056 T51298 T51190 Upregulated in Young Skin Protein containing sh3 domain, sh3gl1 15964 70091 T51315 T51210 Upregulated in Young Skin Hzf3 mRNA for zinc finger protein 17713 71626 T57959 T57877 Upregulated in Old Skin KIAA0183 7544 78252 T50868 T50714 Upregulated in Young Skin Activity and neurotransmitter-induced early gene 6 18011 112913 T75569 T75570 Upregulated in Young Skin (ania-6) mRNA, 3utr Gamma interferon induced monokine 1775 117057 T72007 T87846 Upregulated in Young Skin Lymphotoxin-beta receptor 2974 124034 R02676 R02558 Upregulated in Young Skin Cathepsin O 887 127933 R09047 R08939 Upregulated in Young Skin Ls183984 183984 130216 R22609 R22610 Upregulated in Old Skin Cadherin-11 761 135048 R33891 R33006 Upregulated in Old Skin Homeobox protein hox-B5 2311 135050 R33892 R33007 Upregulated in Young Skin Ls56239 56239 139426 R64493 R65590 Upregulated in Young Skin Glucocorticoid receptor 1836 140925 R66589 R66590 Upregulated in Young Skin Plasma glutathione peroxidase 56887 141629 R69203 R69089 Upregulated in Young Skin Ls25467 25467 145770 R78437 R78438 Upregulated in Old Skin Ls21950 21950 146259 R79054 R78953 Upregulated in Old Skin Ls56260 56260 149460 H00195 H00156 Upregulated in Young Skin Endothelial transcription factor gata-2 1485 149809 R82780 H00625 Upregulated in Young Skin Cartilage glycoprotein-39 859 154966 R55530 R55531 Upregulated in Young Skin Sialyltransferase sthm (sthm) 14338 161509 H25621 H25574 Upregulated in Young Skin YI-1 protein 5195 165884 R88054 R88055 Upregulated in Young Skin Vascular endothelial growth factor B 5106 167296 R90829 R90830 Upregulated in Young Skin Ls138741 138741 219851 H85174 H85134 Upregulated in Young Skin Cyclic nucleotide-gated cation channel cng4 1130 220096 H82535 H82536 Upregulated in Young Skin Peripheral plasma membrane protein cask 6883 223193 H85584 H85585 Upregulated in Young Skin Spl40 protein 4494 229723 H66483 H66484 Upregulated in Young Skin Ls27742 27742 230267 H94947 H94895 Upregulated in Young Skin Endothelial cell protein C/apc receptor (epcr) 10373 252297 H87674 H87172 Upregulated in Young Skin Pl90-B (Pl90-B) 14382 269753 N36267 N24811 Upregulated in Young Skin Clone 23938 6003 271640 N43768 N35014 Upregulated in Young Skin Nonhistone chromosomal protein hmg-14 3454 279792 N50219 N49105 Upregulated in Young Skin Sodium-independent organic anion transporter 4460 289706 N79851 N62948 Upregulated in Young Skin Steroid receptor coactivator-1 7575 297675 N98852 N69880 Upregulated in Young Skin Ls29574 29574 297715 W56046 N68375 Upregulated in Old Skin Glucocorticoid receptor repression factor 1 1837 430335 AA010526 AA010440 Upregulated in Old Skin Vascular cell adhesion protein 1 5105 471101 AA034346 AA033639 Upregulated in Old Skin Ls23999 23999 471785 AA035191 AA035192 Upregulated in Old Skin Ls18019 18019 525206 AA069071 AA069007 Upregulated in Young Skin Ls139152 139152 544542 AA075102 AA074949 Upregulated in Young Skin Mouse mRNA for ly-G alloantigen (ly-6E.1) 56988 544787 AA075232 AA075070 Upregulated in Young Skin Osteonectin 4495 544914 AA075472 AA075473 Upregulated in Old Skin Ubiquitin carboxyl-terminal hydrolase unp 4994 546803 AA083145 AA082988 Upregulated in Young Skin Uroporphyrinogen decarboxylase 5082 648208 AA206966 AA206794 Upregulated in Young Skin Ls19427 19427 725493 AA293375 AA398522 Upregulated in Young Skin KIAA0061 8439 731728 AA417125 AA417084 Upregulated in Young Skin Ls29701 29701 755434 AA419043 AA423797 Upregulated in Old Skin Zinc finger protein gli3 57227 767447 AA418124 AA417948 Upregulated in Old Skin Vasoactive intestinal polypeptide receptor 2 160040 768352 AA495891 AA424999 Upregulated in Old Skin Ls120610 120610 772218 AA404393 AA404386 Upregulated in Young Skin Cartilage homeoprotein 1 860 773093

AA425489 AA425284 Upregulated in Young Skin Butyrophilin (bt3.3) 16807 118997 T92875  
T92784 Upregulated in Young Skin cAMP-dependent protein kinase type II-alpha 821  
34474 R23436 Upregulated in Young Skin regulatory chain Osteocalcin 160416 37522  
R34738 R49611 Upregulated in Young Skin A-kinase anchor protein (akap100) 5391 40844  
R55867 R55786 Upregulated in Young Skin Diacylglycerol kinase eta 4088 40705 R55906  
R55821 Upregulated in Young Skin S-adenosyl homocysteine hydrolase homolog 6979  
41910 R59666 R59606 Upregulated in Young Skin (xpvkona) Thrombin receptor 4687 43099  
R59933 R59934 Upregulated in Young Skin Serine/threonine protein srpk2 16762 43108  
R59847 R59741 Upregulated in Young Skin Inositol 1,3,4-trisphosphate 5/6-kinase  
15469 139207 R68716 R68663 Upregulated in Old Skin Mouse double minute 2, human  
homolog of; p53- 144054 147075 R80343 R80235 Upregulated in Old Skin binding protein  
Tyrosine-protein kinase receptor ufo 4964 49318 H15336 H15718 Upregulated in Young  
Skin Glucokinase regulatory protein 1838 193524 H47437 H47348 Upregulated in Old  
Skin Transcription factor sox-9 4795 240393 H90100 H90010 Upregulated in Young Skin  
Mevalonate kinase 3126 258570 N40752 N30046 Upregulated in Young Skin Fork head  
protein 6904 273876 N46478 N38735 Upregulated in Young Skin Macrophage colony  
stimulating factor i receptor 2997 277866 N64188 N64189 Upregulated in Young Skin  
Neurosin 6348 283418 N57606 N52785 Upregulated in Young Skin Ls19503 19503 293309  
N91739 N64725 Upregulated in Young Skin Death-associated protein kinase 1 1257  
341971 W60209 W60210 Upregulated in Young Skin CDk-activating kinase assembly factor  
mat1 926 380676 AA053721 AA053712 Upregulated in Young Skin Thymidylate kinase 33335  
469802 AA028119 AA028116 Upregulated in Young Skin Maxp1 19495 550298 AA085552  
AA098816 Upregulated in Young Skin DNA topoisomerase II, beta isozyme 1356 28513  
R14153 R40448 Upregulated in Young Skin Ls39933 39933 42582 R59899 R59900  
Upregulated in Young Skin Son; putative DNA binding protein 12319 781752 AA431673  
Upregulated in Young Skin M-protein; skeletal muscle 165kd protein 2994 300219  
W07234 N78805 Upregulated in Old Skin Zinc finger protein 32 5247 307904 W21271  
N93033 Upregulated in Young Skin Deubiquitinating enzyme (ubhl) 30421 328242 W39452  
W38373 Upregulated in Young Skin Protein D52 3966 360768 AA016984 AA016250  
Upregulated in Old Skin Ls40090 40090 363723 AA020848 AA020825 Upregulated in Young  
Skin Ls49645 49645 415692 W78862 W84716 Upregulated in Young Skin Fanconi anemia  
group C protein 1615 428817 AA004738 AA004687 Upregulated in Young Skin Bos taurus  
vacuolar proton pump subunit sfd alpha 22220 429472 AA007653 AA007654 Upregulated in  
Young Skin isoform (sfd)